Management of trauma patients with life-threatening hemorrhage

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CHAPTER 7

The role of recombinant factor VIIa in the treatment of life-threatening hemorrhage in blunt trauma

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Abstract

Background

Recombinant Factor VIIa (rFVIIa) is a novel hemostatic agent originally developed to treat bleeding in hemophiliacs. Several case reports suggest effectiveness of rFVIIa in the treatment of patients without pre-existing bleeding disorders. The aim of this study was to evaluate treatment with recombinant (rFVIIa) in blunt trauma patients with uncontrolled bleeding, in particular with respect to allogeneic blood transfusion.

Patients and Methods

This study was designed as a retrospective case review. Consecutive patients with life-threatening uncontrolled bleeding due to blunt trauma who were treated with rFVIIa were selected. Data were obtained from medical records.

Results

A total of eight blunt trauma patients were treated with rFVIIa for uncontrolled bleeding. After treatment the need for transfusion of packed red blood cells (PRBC) decreased significantly from 31.3 ± 15.8 units to 6.1 ± 6.8 units (P=0.003), fresh frozen plasma (FFP) from 13.3 ± 6.6 units to 5 ± 6.3 units (P=0.02), and platelets (PLTs) from 3.6 ± 1.8 units to 1.5 ± 2.3 units (P=0.01). Three patients died of non-bleeding complications. The other five fully recovered.

Conclusion

Treatment with rFVIIa reduced or stopped bleeding in all patients. No adverse events were registered. Prospective studies are mandatory to elucidate the role of rFVIIa in blunt trauma.

Introduction

Almost half of all trauma deaths are caused by exsanguinations.[1-3] Percentages may be even higher if late complications as multiple systems organ dysfunction are attributed to excessive hemorrhage requiring massive transfusion.[2] Hemorrhage control and restoration of circulating blood volume are the therapeutic goals in the bleeding trauma patient.[4] Treatment of hemorrhagic shock in the pre-hospital phase is limited and based on stopping a compressible bleeding by direct external pressure, closure of wounds and reduction and/or splinting of fractures. Volume resuscitation with crystalloids, colloids and/or transfusion of blood products[5,6] to preserve acceptable vital signs is started on scene, followed by rapid transport to the hospital.[7] In-hospital treatment is based on controlling hemorrhage by performing 'damage control' surgical procedures and ongoing resuscitation by massive transfusion of blood products.[8-11] Since especially blunt trauma may result in diffuse bleeding, surgical measures to control the bleeding may be difficult to perform. In addition, due to persistent bleeding, hypothermia and metabolic acidosis, a profound coagulopathy can occur, which will aggravate the bleeding and may be lethal. This process is directly related to the severity of traumatic injury.[12,13] Case reports suggest that treatment with recombinant coagulation factor VIIa (rFVIIa, Novoseven®, NovoNordisk Bagsvaerd, Denmark) might be beneficial trauma subjects with persistent life-threatening hemorrhage.[13-16] Since most case series of severe bleeding are mainly based on patients with penetrating wounds, we analyzed our data with rFVIIa in blunt trauma subjects with potential lethal bleeding.

Patients and Methods

From 2001 to 2003, all patients with blunt traumatic injury who were treated with rFVIIa were identified in the Nijmegen University Hospital and in the Rijnstate Hospital Arnhem using the ICU registry. These level 1 (Nijmegen) and level 2 (Arnhem) trauma centers are located in a rural area of the Netherlands. Data were extracted from each patient's medical record in order to document the effect of rFVIIa administration on the patient's clinical condition. The obtained data consisted of trauma mechanism, type of injuries, Revised Trauma Score (RTS), Injury Severity Score (ISS)[17], systolic blood pressure (SBP), body temperature (BT), arterial pH, base deficit (BD) on admission and survival. In addition, information on hemostatic surgical or radiological (selective arterial embolization) procedures was obtained. Amounts of transfused packed red blood cells (PRBC), fresh frozen plasma (FFP) or platelets (PLTs)were compared before and 24 hours after the administration of rFVIIa. Results are expressed as mean ± SD. For this comparison, statistical analysis was performed using a paired Student's T-test. The differences were considered significant at a probability level of 95% ($P<0.05$). Dosing and timing of rFVIIa administration and possible adverse effects of treatment with rFVIIa were registered.

Results

Eight trauma patients were treated with rFVIIa due to uncontrolled bleeding (Table 1). All patients had sustained blunt trauma resulting in bleeding from abdominal and/or thoracic injuries and/or bone fractures. Five patients were intubated before admission. The mean RTS was 10 ± 1 and ISS 34 ± 15. On admission, most patients were hypothermic (body temperature <36°C) and had metabolic acidosis indicated by an arterial pH less than 7.35 and a BD of less than –2. Five patients were hypotensive (SBP <90 mmHg). All patients underwent at least one surgical or radiological (embolization) procedure before administration of rFVIIa (Table 2). Two patients underwent a hemostatic procedure after rFVIIa. In patient #3 treatment with rFVIIa facilitated a successful surgical re-intervention (right hemi-hepatectomy). In patient #7, bleeding as indicated by the need for transfusion was decreased in such a way that other hemostatic procedures could be performed (abdominal packing and embolization of a pudendal artery; Table 2). rFVIIa was administered at 9-38 hours after trauma in doses varying from 55 to 90 μg/kg. In patient #2 a second dose of rFVIIa was administered 14 hours after the first dose because of an increase in chest drain production after an initial decrease (Table 2). The need for transfusion of PRBC decreased significantly from 31.3 ± 15.8 units to 6.1 ± 6.8 units (P=0.003), FFP from 13.3 ± 6.6 units to 5 ± 6.3 units (P=0.02), and PLTs from 3.6±1.8 units to 1.5±2.3 units (P=0.01; Table 2). In all patients the critical bleeding stopped. Two patients died of ARDS and/or MODS and a third patient died of the consequences of traumatic brain injury.

Table 1. Characteristics of blunt trauma patients with uncontrolled bleeding

Patient	Sex	Age (years)	Mechanism of injury	Intubated before admission	Major injuries	RTS	ISS	BT (°C)	SBP (mmHg)	pH	BE
1	M	20	MVA (car vs. obstacle)	No	Extensive liver lacerations (Grade V)	12	27	-	95	7.32	-8
2	M	44	Suicide attempt (jump in front of train)	No	Hemopneumothorax , thoracic wall injury, unstable pelvic fracture, femoral neck fracture, traumatic amputation of the leg	9	43	-	60	-	-
3	F	14	Horse stampede	Yes	Extensive liver lacerations with inferior caval vein involvement (Grade V)	11	30	33.8	80	7.19	-14
4	M	23	MVA (car vs. obstacle)	Yes	Flail chest, thoracic wall injury, diaphragmatic rupture	12	21	34	110	7.25	-6.8
5	M	19	MVA (bicyclist vs. car)	Yes	Extensive liver lacerations (Grade V), severe cerebral injury	8	59	33	90	7.18	-12.4
6	M	25	MVA (motorcyclist vs. car)	Yes	Liver laceration (Grade II), diaphragmatic rupture, thoracic wall injury, instable pelvic fracture, femoral fracture, leg fracture, humeral fracture	9	41	35.2	60	7.08	-16.7
7	M	54	Horese back riding	No	Unstable pelvic disruption	10	11	36	80	7.21	-9
8	M	32	Grabbed by mechanical excavator	Yes	Splenic rupture (Grade IV), kidney laceration (Grade II), hemothorax, thoracic wall injury, thoracolumbar spine injury	11	36	35	80	7.23	-5.9
Mean						10	34				
SD						1	15				

RTS: Revised Trauma Score; ISS: Injury Severity Score[3]; BT: body temperature; SBP: systolic blood pressure; all values on admission. MVA: motor vehicle accident.

Table 2. Results of administration of recombinant factor VIIa on transfusion of blood products and clinical outcome

Patient	rVIIa timing (hr)	Dosing (mcg/kg)	Previous hemostatic procedures	Procedures after rFVIIa	Before PRBC	FFP	PLT	After PRBC	FFP	PLT	ICU (days)	Survival
1	9	60	Liver packing (twice)	None	32	21	3	2	1	0	2	Dead (MODS)
2	26 (1^{o} dose); 38 (2^{nd} dose)	60	External fixation pelvis, embolization internal iliac artery, thoracotomy	None	34	23	4	1	0	0	54	Alive
3	20	55	Liver packing (twice)	Hemihepatectomy	31	16	6	21	20	7	16	Alive
4	3.5	90	Thoracotomy	None	25	10	3	4	4	0	5	Alive
5	3.5	90	Liver packing	None	9	6	2	6	2	1	8	Dead (severe TBI)
6	5.5	90	Liver packing, thoracotomy, external fixation pelvis and multiple long bone fractures	None	64	15	6	0	4	1	8	Dead (ARDS /MODS)
7	10	90	Symphysiodesis (internal fixation)	Abdominal packing, embolization pudendal artery	35	10	4	10	6	2	14	Alive
8	6.5	90	Splenectomy, abdominal packing, thoracotomy	None	20	5	1	5	3	1	13	Alive
Mean					31.3	13.3	3.6	6.1	5.0	1.5		
SD					15.8	6.6	1.8	6.8	6.3	2.3		
P-value (versus PRBC, FFP or PLTs transfusion before rFVIIa, respectively)								0.003	0.02	0.01		

rFVIIa timing, time elapsed between accident and administration of rFVIIa; PRBC: packed red blood cells; FFP: fresh frozen plasma; PLTs: platelet; ICU: Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome; MODS: Multiple Organ Dysfunction Syndrome; TBI: traumatic brain injury.

Discussion

In massive hemorrhage due to trauma, surgical hemostasis has the highest priority.[10] Operative procedures using cautery, clips, suture, ligature, hemostatic sealants, (partial) resection of bleeding solid organs and/or packing with gauzes are in most cases sufficient to control the bleeding. Especially in blunt trauma, diffuse excessive bleeding may persist, which may be difficult to control surgically. In this situation systemic coagulation defects arise by loss of platelets and coagulation factors due to bleeding and dilution of these elements upon massive transfusion of PRBC and plasma substitutes. Acidosis and hypothermia further worsen coagulopathy and potentially aggravate the bleeding. Correcting acidosis, body temperature, and transfusion of blood components (PRBC, platelets) and coagulation factors (FFP) are the conventional treatment modalities to control this diffuse bleeding. In trauma patients with excessive bleeding, where this conventional therapy or damage control surgery fails, administration of rFVIIa seems highly effective as reported in case reports. In the presented case series, blunt trauma was the mechanism of injury in all patients. In our series three out of 8 patients died, but excessive bleeding was reduced or stopped in such a way that all the patients survived the initial damage control period. Overall survival in such a small series cannot be expressed in TRISS (Trauma and Injury Severity Score).[18] Taken into account that five patients were intubated before admission, the use of standard TRISS might even not be applicable to the assessment of these patients.[9] In one series of Martinowitz *et al.* three out of seven patients died of other reasons than exsanguinations.[13] In another series of Martinowitz *et al.* thirteen out of 19 patients survived.[16] However, 4 patients exsanguinated within 24 hours and two patients died of late complications. Dutton *et al.* presented a series, in which two out of five patients died through uncontrollable bleeding, but these two patients sustained lethal initial injuries.[20] Thus, prospective studies have to elucidate the role of rFVIIa in survival of bleeding blunt trauma subjects.

In our cases, the dose of rFVIIa and the timing of administration were not based on a standard protocol but based on decisions of individual physicians. rFVIIa was administered at a time where no other options for treatment, surgical or medical (including angioembolization), were left and bleeding would have been lethal. The need for administration of PRBC, PLTs, and FFP within 24 h after treatment with rFVIIa was significantly reduced. Our results confirm previous reports that the use of rFVIIa-therapy might be beneficial in exsanguinating trauma patients, but exceed other reports since our series involve only blunt trauma patients. Blunt injury more often leads to diffuse bleeding, in which surgical

hemostasis might be more difficult to achieve. So, treatment with rFVIIa may be especially effective in these patients. rFVIIa was originally developed for treatment of hemorrhages in hemophiliacs with inhibitors to factors VIII or IX. It induces hemostasis at the site of tissue injury by complex formation with locally abundant tissue factor without systemic activation of coagulation.[21] Administration of rFVIIa might be beneficial in trauma patients with life-threatening bleeding.[13,14,15,20,22]

Early administration (home treatment) of rFVIIa in hemophiliacs is effective and requires a smaller number of doses.[23] In trauma, there is no experience with administration of rFVIIa in an earlier stage of massive hemorrhage, e.g. at the trauma scene. The optimal dosage of rFVIIa is another area of uncertainty. Doses varying from 80 to 212 mcg/kg have been used in trauma patients.[13,20] Some patients in our series were treated with low doses of rFVIIa (60 mcg/kg) but with comparable results. In hemophiliacs undergoing major surgery 90 mcg/kg is recommended[24], but in a recently published randomized controlled trial among patients with normal hemostasis undergoing prostatectomy a beneficial effect of 40 mcg/kg was shown.[25] Higher doses of rFVIIa generate a more rapid thrombin burst producing a more stable clot that is less prone to fibrinolysis. Thus, in massively bleeding trauma patients with coagulopathy the effective dose may be higher. The exact dose and timing of rFVIIa treatment remain to be established. The incidence of thrombotic complications due to rFVIIa seems low. In more than 2,500 published episodes of bleeding in which rFVIIa was administered, 14 patients (0.7%) had a thrombotic event.[26] Most of these patients had risk factors for thrombosis like immobilization or surgery. Since these data stem from patients with pre-existent coagulation abnormalities, the safety of this treatment in the general population has to be established. In our cases, transfusion of blood products occurred without a clear strategy. A standardized transfusion strategy with a fixed ratio of PRBC, FFP and PLTs is of utmost importance to improve hemostasis and may decrease further transfusion need. Transfusion of blood products is an independent risk factor for post-injury MODS[27] and a clear dose-dependent correlation exists between transfusions of RBC and the development of infections in trauma patients.[28] Thus, treatment with rFVIIa might prevent complications by reducing transfusion needs.

Conclusions

Administration of rFVIIa seems to be beneficial in blunt trauma patients with uncontrolled bleeding, but the optimal timing and dose of administration remain to be established. Also, prospective randomized trials with emphasis on safety, survival rates and transfusion consumption are needed to elucidate the role of rFVIIa as an adjunct to bleeding control in blunt trauma.

References

1. Baker CC, Oppenheimer L, Stephens B, Lewis FR, Trunkey DD. Epidemiology of trauma deaths. Am J Surg 1980;140: 144-50.
2. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, Pons PT. Epidemiology of trauma deaths: a reassessment. J Trauma 1995;38: 185-93.
3. Shackford SR, Mackersie RC, Holbrook TL, Davis JW, Hollingsworth-Fridlund P, Hoyt DB, Wolf PL. The epidemiology of traumatic death. A population-based analysis. Arch Surg 1993;128: 571-5.
4. Vaslef SN, Knudsen NW, Neligan PJ, Sebastian MW. Massive transfusion exceeding 50 units of blood products in trauma patients. J Trauma 2002;53: 291-5.
5. Barkana Y, Stein M, Maor R, Lynn M, Eldad A. Prehospital blood transfusion in prolonged evacuation. J Trauma 1999;46: 176-80.
6. Garner AA, Bartolacci RA. Massive prehospital transfusion in multiple blunt trauma. Med J Aust 1999;170: 23-5.
7. McSwain Jr NE, Frame S, Paturas JL (Eds) PHTLS, Basic and Advanced Prehospital Trauma Life Support. Mosby, St. Louis, 1999: 40-51.
8. Asensio JA, McDuffie L, Petrone P, Roldań G, Forno W, Gambaro E, Salim A, Demetriades D, Murray J, Velmahos G, Shoemaker W, Berne TV, Ramicone E, Chan L. Reliable variables in the exsanguinated patient which indicate damage control and predict outcome. Am J Surg 2001;182: 743-51.
9. Collicott PE, Hughes I. Training in advanced trauma life support. JAMA 1980;243: 1156-9.
10. Mattox KL, Feliciano DV, Moore EE. (Eds) Trauma (4th edn.). McGraw-Hill, 2000; 907-10.
11. Shapiro MB, Jenkins DH, Schwab CW, Rotondo MF. Damage control: collective review. J Trauma 2000;49: 969-78.
12. Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. J Trauma 1997;42: 857-61.
13. Martinowitz U, Kenet G, Segal E, Luboshitz J, Lubetsky A, Ingerslev J, Lynn M. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. J Trauma 2001;51: 431-8.
14. Kamphuisen PW, van den Akker JM, Kaasjager HAH, Bloemen TI. Control of life-threatening pulmonary bleeding with activated recombinant factor VII. Am J Med 2002;112: 332-3.
15. Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. Lancet 1999;354: 1879.
16. Martinowitz U, Kenet G, Lubetski A, Luboshitz J, Segal E. Possible role of recombinant activated factor VII (rFVIIa) in control of hemorrhage associated with massive trauma. Can J Anaesth 2002;49: S15-20

17. Baker SP, O'Neill B, Haddon W Jr, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974;14: 187-96,
18. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. Trauma Score and the Injury Severity Score. J Trauma 1987;27: 370-8.
19. Davis EG, MacKenzie EJ, Sacco WJ, Bain LW Jr, Buckman RF Jr, Champion HR, Lees PS. A new „TRISS-like" probability of survival model for intubated trauma patients. J Trauma 2003;55: 53-61.
20. Dutton RP, Hess JR, Scalea TM. Recombinant factor VIIa for control of hemorrhage: early experience in critically ill trauma patients. J Clin Anesth 2003;15: 184-8.
21. Monroe DM, Hoffman M, Oliver JA, Roberts HR. Platelet activity of high-dose factor VIIa is independent of tissue factor. Br J Haematol 1997;99: 542-7.
22. O'Neill PA, Bluth M, Gloster ES, Wali D, Priovolos S, DiMaio TM, Essex DW, Catanese CA, Strauss RA. Successful use of recombinant activated factor VII for trauma-associated hemorrhage in a patient without preexisting coagulopathy. J Trauma 2002;52: 400-5.
23. Santagostino E, Gringeri A, Mannucci PM. Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: the advantages of early intervention. Br J Haematol 1999;104: 22-6.
24. Shapiro AD, Gilchrist GS, Hoots WK, Cooper HA, Gastineau DA. Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. Thromb Haemost 1998;80: 773-8.
25. Friederich PW, Henny CP, Messelink EJ, Geerdink MG, Keller T, Kurth KH, Büller HR, Levi M. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. Lancet. 2003;361: 201-5.
26. Roberts HR. Recombinant factor VIIa (Novoseven) and the safety of treatment. Semin Hematol 2001;38: 48-50.
27. Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. Arch Surg 1997;132: 620-4.
28. Claridge JA, Sawyer RG, Schulman AM, McLemore EC, Young JS. Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. Am Surg 2002;68: 566-72.